

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



10/528691



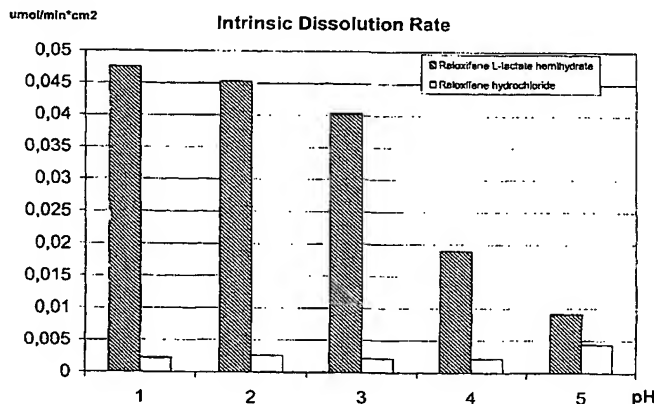
(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/029046 A3

- (51) International Patent Classification⁷: C07D 409/12, A61K 31/445, 31/381, A61P 35/00, 19/00 // (C07D 409/12, 333:56, 295:08)
- (21) International Application Number: PCT/DK2003/000645
- (22) International Filing Date: 30 September 2003 (30.09.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: PA 2002 01450 30 September 2002 (30.09.2002) DK
- (71) Applicant (for all designated States except US): A/S GEA FARMACEUTISK FABRIK [DK/DK]; Kanalholmen 8-12, DK-2650 Hvidovre (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KARUP, Gunnar, Leo [DK/DK]; Bremensgade 39, DK-2300 Copenhagen S (DK). PEDERSEN, Søren, Bols [DK/DK]; Vesterkærsvvej 7, DK-2650 Hvidovre (DK).
- (54) Title: NOVEL RALOXIFENE ACID ADDITION SALTS AND/OR SOLVATES THEREOF, IMPROVED METHOD FOR PURIFICATION OF SAID RALOXIFENE ACID ADDITION SALTS AND/OR SOLVATES THEREOF AND PHARMACEUTICAL COMPOSITIONS COMPRISING THESE
- (74) Agents: RASMUSSEN, Preben et al.; International Patent-Bureau A/S, Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).
- (81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declaration under Rule 4.17:
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,

[Continued on next page]



(57) Abstract: Raloxifene acid addition salts or solvates thereof, having improved dissolution properties in media comprising hydrochloric acid are described. The disclosed acid addition salts or solvates thereof show an improved bioavailability in media comprising hydrochloric acid, such as the gastric juice. The acid addition salts or solvates thereof are addition salts or solvates of raloxifene and a pharmaceutical acceptable acid selected among succinic acid, lactic acid, malonic acid or sulphuric acid. Further, crystalline forms of the raloxifene salts and solvates thereof are disclosed. The raloxifene acid addition salts and/or solvates thereof are useful for the preparation of pharmaceutical composition for oral administration capable of fast and reliable release of the active ingredients in the stomach of the patient, in particular for the treatment of cancer or osteoporosis, or for inhibiting cartilage degradation. A new method for preparation of raloxifene lactate is also disclosed.

WO 2004/029046 A3



CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

14 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 A61K31/445 A61K31/381 A61P35/00 A61P19/00
 //(C07D409/12,C07D333:56,295:08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 062 503 A (LILLY CO ELI) 13 October 1982 (1982-10-13) page 7, line 24 -page 8, line 11 page 15, line 4 - line 17; claims 2-4 ---	1-20
A	EP 0 584 952 A (LILLY CO ELI) 2 March 1994 (1994-03-02) page 5, line 3 - line 25; claims ---	1-20
A	EP 0 652 002 A (LILLY CO ELI) 10 May 1995 (1995-05-10) page 3, line 9 - line 29; claims ---	1-20
A	EP 0 875 511 A (LILLY CO ELI) 4 November 1998 (1998-11-04) page 4, line 10 - line 29 page 4, line 43; claims ---	1-20
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 December 2003

Date of mailing of the international search report

06. 09. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

GERD STRANDELL /EÖ

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 826 682 A (LILLY CO ELI) 4 March 1998 (1998-03-04) page 4, line 51 -page 5, line 22; claims ---	1-20
A	WO 97 35571 A (STRATFORD ROBERT E JR ;DALDER BRIAN W (US); LILLY CO ELI (US); LUK) 2 October 1997 (1997-10-02) claims page 1, line 4 -page 2, line 13 page 3, line 32 -page 4, line 5 ---	1-20
A	WO 00 35485 A (KANANEN MIKKO ;AF URSIN KAIJA (FI); KIESVAARA JUHA (FI); KORTESUO) 22 June 2000 (2000-06-22) page 1, line 7 page 3, line 13 -page 4, line 2 claims ---	1-20
A	WO 96 09045 A (LILLY CO ELI ;LABELL ELIZABETH SMITH (US); LUKE WAYNE DOUGLAS (US)) 28 March 1996 (1996-03-28) the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0062503	A	13-10-1982	AT 17243 T	15-01-1986
			AT 14429 T	15-08-1985
			AU 555658 B2	02-10-1986
			AU 8226582 A	07-10-1982
			BG 37378 A3	15-05-1985
			CS 227348 B2	16-04-1984
			DD 201794 A5	10-08-1983
			DD 201793 A5	10-08-1983
			DE 3264853 D1	29-08-1985
			DE 3268227 D1	13-02-1986
			DK 151282 A	04-10-1982
			DK 151382 A	04-10-1982
			EG 15610 A	30-06-1986
			EP 0062503 A1	13-10-1982
			EP 0062504 A1	13-10-1982
			EP 0062505 A1	13-10-1982
			ES 8304116 A1	16-05-1983
			ES 8307240 A1	16-10-1983
			FI 821160 A	04-10-1982
			FI 821161 A	04-10-1982
			GB 2097392 A ,B	03-11-1982
			GB 2097788 A ,B	10-11-1982
			GB 2096608 A ,B	20-10-1982
			GR 76468 A1	10-08-1984
			GR 78364 A1	26-09-1984
			HU 191084 B	28-01-1987
			HU 191353 B	27-02-1987
			IE 53187 B1	17-08-1988
			IL 65378 A	28-02-1986
			JP 57181081 A	08-11-1982
			KR 8501881 B1	28-12-1985
			KR 8501882 B1	28-12-1985
			MX 9203117 A1	01-07-1992
			NZ 200204 A	31-05-1985
			PH 18628 A	23-08-1985
			PL 235751 A1	22-11-1982
			PL 235752 A1	22-11-1982
			PT 74692 A ,B	01-05-1982
			PT 74693 A ,B	01-05-1982
			RO 84584 A1	17-07-1984
			SU 1155157 A3	07-05-1985
			US 4418068 A	29-11-1983
			ZA 8202247 A	30-11-1983
<hr/>				
EP 0584952	A	02-03-1994	AT 152351 T	15-05-1997
			AU 4422193 A	03-02-1994
			BG 61429 B1	29-08-1997
			BG 97982 A	25-04-1994
			BR 9303013 A	16-02-1994
			CA 2101356 A1	29-01-1994
			CN 1088205 A ,B	22-06-1994
			CY 2044 A	30-04-1998
			CZ 9301498 A3	13-04-1994
			DE 69310288 D1	05-06-1997
			DE 69310288 T2	11-09-1997
			DK 584952 T3	13-10-1997
			EP 0584952 A1	02-03-1994
			EP 0781555 A1	02-07-1997

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0584952	A		ES 2102602 T3	01-08-1997
			GR 3024171 T3	31-10-1997
			HK 90197 A	01-08-1997
			HU 65707 A2	28-07-1994
			IL 106450 A	31-12-1999
			JP 2749247 B2	13-05-1998
			JP 6199665 A	19-07-1994
			JP 3162662 B2	08-05-2001
			JP 10114656 A	06-05-1998
			KR 161300 B1	01-12-1998
			LU 90334 A9	23-02-1999
			MX 9304432 A1	31-05-1994
			NO 932650 A	31-01-1994
			NZ 248210 A	24-06-1997
			NZ 314686 A	28-07-2000
			PH 30032 A	08-11-1996
			PL 299814 A1	07-02-1994
			RO 113212 B1	29-05-1998
			RU 2104697 C1	20-02-1998
			SG 45315 A1	16-01-1998
			US 5393763 A	28-02-1995
			US 5457117 A	10-10-1995
			US 5534527 A	09-07-1996
			ZA 9305283 A	23-01-1995

EP 0652002	A	10-05-1995	US 5418252 A	23-05-1995
			AT 199642 T	15-03-2001
			AU 676375 B2	06-03-1997
			AU 7578994 A	04-05-1995
			CA 2118094 A1	16-04-1995
			CN 1106260 A ,B	09-08-1995
			CZ 9402534 A3	17-05-1995
			DE 69426855 D1	19-04-2001
			DE 69426855 T2	30-08-2001
			DK 652002 T3	17-04-2001
			EP 0652002 A1	10-05-1995
			ES 2154669 T3	16-04-2001
			GR 3035864 T3	31-08-2001
			HU 71249 A2	28-11-1995
			IL 111291 A	26-01-1999
			JP 7188013 A	25-07-1995
			NO 943873 A	18-04-1995
			NZ 264672 A	24-06-1997
			PT 652002 T	29-06-2001
			SI 652002 T1	30-06-2001
			ZA 9408028 A	15-04-1996

EP 0875511	A	04-11-1998	CA 2236254 A1	30-10-1998
			EP 0875511 A1	04-11-1998
			JP 11005789 A	12-01-1999
			US 5994547 A	30-11-1999

EP 0826682	A	04-03-1998	AT 234295 T	15-03-2003
			AU 723987 B2	07-09-2000
			AU 4233597 A	19-03-1998
			BR 9713176 A	08-02-2000
			CA 2263175 A1	05-03-1998
			CN 1244124 A	09-02-2000

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0826682	A	CZ 9900643 A3 DE 69719640 D1 DE 69719640 T2 EA 2022 B1 EP 0826682 A1 HU 0001172 A2 IL 128641 A IN 182940 A1 JP 2002514174 T KR 2000035941 A NO 990914 A NZ 333839 A PL 333356 A1 TR 9900403 T2 WO 9808513 A1 ZA 9707617 A	12-05-1999 17-04-2003 06-11-2003 24-12-2001 04-03-1998 28-06-2001 31-10-2001 14-08-1999 14-05-2002 26-06-2000 25-02-1999 29-06-2001 06-12-1999 21-01-2002 05-03-1998 25-02-1999
WO 9735571	A 02-10-1997	AU 723797 B2 AU 2215497 A BR 9708248 A CA 2250191 A1 CN 1213967 A CZ 9803053 A3 EA 1257 B1 EP 0910369 A1 HU 9902750 A2 ID 19813 A IL 126320 A JP 2000507268 T KR 2000004962 A NO 984444 A NZ 332036 A NZ 333913 A PL 329051 A1 TR 9801915 T2 TW 513421 B WO 9735571 A1 US 2003187025 A1 US 6458811 B1 ZA 9702507 A	07-09-2000 17-10-1997 27-07-1999 02-10-1997 14-04-1999 12-05-1999 25-12-2000 28-04-1999 28-04-2000 06-08-1998 08-08-2001 13-06-2000 25-01-2000 26-11-1998 29-04-1999 25-08-2000 01-03-1999 21-12-1998 11-12-2002 02-10-1997 02-10-2003 01-10-2002 25-09-1998
WO 0035485	A 22-06-2000	FI 982733 A AU 1985500 A CA 2355175 A1 EP 1140196 A1 WO 0035485 A1 JP 2002532437 T NO 20012793 A NZ 512270 A US 2003181530 A1 US 6632841 B1	18-06-2000 03-07-2000 22-06-2000 10-10-2001 22-06-2000 02-10-2002 09-08-2001 31-01-2003 25-09-2003 14-10-2003
WO 9609045	A 28-03-1996	US 5629425 A AP 754 A AT 407988 B AT 154295 A AU 691955 B2 AU 3173095 A	13-05-1997 22-07-1999 25-07-2001 15-12-2000 28-05-1998 04-04-1996

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00645

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9609045	A	AU 692907 B2	18-06-1998
		AU 3173195 A	04-04-1996
		AU 3718695 A	09-04-1996
		BE 1009625 A3	03-06-1997
		BE 1009626 A3	03-06-1997
		BG 62793 B1	31-08-2000
		BG 101242 A	31-03-1998
		BR 9504059 A	24-09-1996
		BR 9504060 A	24-09-1996
		CA 2158399 A1	20-03-1996
		CA 2158400 A1	20-03-1996
		CH 691594 A5	31-08-2001
		CH 691431 A5	31-07-2001
		CH 691478 A5	31-07-2001
		CH 691125 A5	30-04-2001
		CN 1132205 A ,B	02-10-1996
		CN 1127253 A ,B	24-07-1996
		CZ 9502402 A3	17-04-1996
		CZ 9502403 A3	17-04-1996
		DE 19534744 A1	21-03-1996
		DE 19534745 A1	04-04-1996
		DK 2797 A	09-01-1997
		DK 2897 A	09-01-1997
		DK 102795 A	20-03-1996
		DK 102895 A	20-03-1996
		EE 9700055 A	15-08-1997
		ES 2109882 A1	16-01-1998
		ES 2129293 A1	01-06-1999
		FI 954402 A	20-03-1996
		FI 954403 A	20-03-1996
		FR 2724655 A1	22-03-1996
		FR 2732020 A1	27-09-1996
		GB 2293382 A ,B	27-03-1996
		GB 2293602 A ,B	03-04-1996
		GR 1002697 B	22-05-1997
		GR 1002709 B	04-06-1997
		HK 1019009 A1	27-10-2000
		HR 950482 A1	28-02-1998
		HR 950483 A1	31-10-1997
		HU 75033 A2	28-03-1997
		HU 74178 A2	28-11-1996
		IE 950721 A1	20-03-1996
		IE 950722 A1	20-03-1996
		IL 115314 A	29-02-2000